

**EMEA ad hoc WORKING GROUP ON HERBAL MEDICINAL PRODUCTS****Dr. Konstantin Keller, Berlin  
Chairman**

Upon the initiative of the European Commission and the Executive Director of the European Agency for the Evaluation of Medicinal Products (EMEA), and with the support of the EMEA Management Board, an ad hoc Working Group on Herbal Medicinal Products was created at the EMEA in May 1997.

The creation of the group is in line with comparable activities on the international level outside the EU: The 8<sup>th</sup> WHO International Conference of Drug Regulatory Agencies (ICDRA) recommended to create special expert groups for the assessment of herbal medicinal products on a national and on a regional level. In November 1997 a US presidential Commission recommended to include herbal medicinal products in the OTC-registration system and to create a special expert group for herbal medicinal products.

The group aimed at:

- gathering the experience of Member States in the field of herbal medicinal products
- providing guidance for applicants and competent authorities
- preparing recommendations on criteria for the assessment of quality, safety and efficacy of herbal medicinal products
- reviewing existing legislation taking into account the particularities of herbal medicinal products

It should be emphasised that it is not the aim of the group to review the national review or to criticise national approaches in the assessment of herbal medicinal products, but to protect public health by facilitating the approach of truthfully labelled herbal medicinal products to a common European market.

Having had a limited mandate for three meetings from June to November 1997 and a second limited mandate for only two meetings in 1998, it was impossible to address all problems or to find answers to all questions that have accumulated since the introduction of a European pharmaceutical legislation in 1965.

Three areas where the assessment of herbal medicinal products needs clarification were identified:

1. the commerce with crude herbal drugs which are not finished medicinal products;
2. the use of strictly traditional drugs on a limited regional market or used by ethnic minorities and
3. finished medicinal products.

For finished medicinal products the legal framework and the definition of terms related to the problem are clear: Industrially prepared, finished herbal medicinal products fall within the scope of Council Directive 65/65/EEC. They are available in all Member States of the European Union. They have access to the decentralised procedure for marketing authorisations. Major differences in the assessment of Quality, Safety and Efficacy would hinder free circulation of herbal medicinal products in the EU and may represent a risk for consumers.

This is why the group concentrated its work on those finished medicinal products where a community-interest is evident. The two other areas may be discussed in connection with the report of the European Commission that is currently being prepared. After more than 20 years of experience with the regulatory assessment of herbal medicinal products in Germany I am convinced that the problem of the first and second groups of products cannot be resolved by a simple registration comparable to the

registration of homeopathic products, because such an approach is completely inadequate to herbal medicinal products. Nor would a “traditionally used” label protect the European consumer from fraudulent or misleading claims. Tradition cannot be implemented in Member States by European regulations.

The complexity of herbal drug preparations and the interpretation of bibliographic data on safety and efficacy reflecting the experience gathered during long-term use, are best addressed by involving specific expertise and experience. Safety and efficacy of complex biological products, such as herbal medicinal products, are directly linked to pharmaceutical details such as the way of production and the specification of extracts. Thanks to the delegates and experts nominated by all Member States, and the active contribution of the representatives of the European Parliament, the European Commission and the European Pharmacopoeia, this unique, pluridisciplinary expertise was available and a competent and constructive discussion on the legal aspects as well as pharmaceutical, preclinical and clinical aspects was achieved.

EMEA ad hoc Working Group Herbal Medicinal Products		
<i>45 Delegates and Experts</i>		
Austria	Germany	Netherlands
Belgium	Greece	Portugal
Denmark	Ireland	Spain
Finland	Italy	Sweden
France	Luxembourg	United Kingdom
<i>Europ. Parliament</i>	<i>Europ. Pharmacopoeia</i>	
<i>Europ. Commission</i>	EMEA	

At its first three meetings in 1997, the group reviewed the appropriateness of the Notice to Applicants Vol 2A and 2B for herbal medicinal products and the criteria set out in Council Directives for the

demonstration of pharmaceutical quality, pre-clinical safety, and clinical efficacy in the case of marketing authorisation applications for herbal medicinal products. Proposals for clarification of existing legislation and for new guidance were sent out for comment in January 1998. The response to these proposals by scientific organisations and by industry was very positive. Constructive proposals for further improvement were submitted. At the last meeting in July 1998 relevant documents could be finalised and new proposals were sent out for comments by December 1998.

The following topics were addressed during the discussions:

#### Notice to Applicants

The NTA volume 2A: *Administrative requirements, guidance on the operation of the marketing authorisation systems* was reviewed and found adequate for herbal medicinal products.

The NTA volume 2B: *Presentation and content of the application dossier* (version January 1997) needed major clarifications. The group proposed modifications to Part II, to better adapt it to herbal medicinal products. Comments coming from interested parties were discussed and modifications were implemented at the July meeting of this year.

Notice to Applicants of January 1997	
NTA 2A :	<i>Administrative Requirements</i>
NTA 2B, Part I B 1:	<i>Summary of Product Characteristics</i>
NTA 2B, Part I C 1:	<i>Expert Report on Chemical, Pharmaceutical and Biological Documentation</i>
NTA 2B, Part I C 2:	<i>Expert Report on toxico-pharmacological documentation</i>
NTA 2B, Part II:	<i>Chemical, Pharmaceutical and Biological Documentation for Vegetable Medicinal Products</i>
NTA 2B, Part III:	<i>Toxico-pharmacological Documentation</i>

tabulated formats for pharmaceutical expert report included in the NTA were found inadequate for

herbal medicinal products and a proposal for a revised version was released for comments in September 1998. Because the formats for the pharmaceutical expert report are closely linked to the structure of the dossier, the updated proposals for modifications of Part II were sent out for comments again. Chapter I of the NTA, *Marketing Authorisations, Section 4.2 Bibliographic Applications* was discussed. The group found that scientific monographs for herbal drugs drafted by the European Scientific Co-operative on Phytotherapy (ESCOP) and the World Health Organisation (WHO) offer a valuable and updated overview of published scientific literature. Such monographs may be used, together with the supporting literature, in support of the demonstration of the safety and efficacy of a herbal medicinal product in a bibliographical application in accordance with Article 4.8 (a)ii. These monographs may help to avoid duplication of work and bring about gradual harmonisation in the evaluation of herbal medicinal products. The use of these monographs should, however, not preclude the implementation of new research and scientific developments.

#### Notice to Applicants

*Comments and proposals for revision  
NTA 2A, Marketing Authorisations, 4.2*

... Scientific monographs ... (e.g. those drafted by the European Scientific Co-operative on Phytotherapy (ESCOP) and the World Health Organisation (WHO) for herbal drugs) offer **a valuable and updated overview on published scientific literature**, which together may be used in support of the demonstration of the safety and efficacy of a medicinal product in a bibliographical application in accordance with Article 4.8 (a)ii. These monographs may **help to avoid duplication** of work and **bring about gradual harmonisation** in the evaluation of medicinal products, e.g. herbal medicinal products. Therefore the Commission and Member States recommend that both applicants and competent authorities should make use of these monographs. The use of these monographs should not preclude the future development or implementation of results of new clinical trials.

The representative of the Commission informed the group that the final proposals of the group will be made available in the homepage of the DG III. The commission will inform the NTA working party on the group's proposals and implement them in the NTA as soon as possible.

This way of implementation of the recommenda-

tions of the group is a pragmatic one and the Commission's strong support to our work has to be underlined. In my view it does not make sense to establish a group of qualified experts and then to refer all proposals of the group to the different conventional groups that do not have that specific experience with herbal products. Such a repetition of efforts will be a source of permanent confusion rather than it will improve harmonisation.

#### Quality guidance

In the field of quality, the group reviewed existing guidance for Good Manufacturing Practice (GMP), which was considered acceptable. Minor modifications would suffice for updating Annex 7 'Manufacture of Herbal Medicinal Products' of GMP.

It was indicated that a consistent quality of herbal drugs may need more detailed information on aspects of agricultural production. The selection of seeds, conditions of cultivation and harvesting represent an important aspect in producing a reproducible quality of herbal drugs. Ongoing discussions on Good Agricultural Practices (GAP) for medicinal plants should be monitored and cross-references should be included in the Annex to the GMP as soon as a consensus on GAP is obtained. The ongoing discussion on the GMP of starting materials should be monitored in this respect.

#### Good Manufacturing Practices (GMP)

*Annex 7 Manufacture of Herbal Medicinal Products.*

##### *Principle*

A consistent quality of herbal drugs may need more detailed definitions of aspects of agricultural production. Ongoing discussions on Good Agricultural Practices (GAP) for medicinal plants should be monitored

The requirements for the pharmaceutical documen-

tation needed an update, in particular the former Note for Guidance "Quality of Herbal Remedies". After discussion of comments received from interested parties at the July meeting, final proposals for modification of the Annex to the GMP guidelines and a new note for guidance "Quality of herbal medicinal products" were presented to the CPMP in September 1998 for information and were released by the EMEA via the Internet. The group agreed on a terminology for herbal medicinal products. Terms such as *herbal remedies*, *vegetable drugs*, etc. should be replaced by the terms *herbal drug*, *herbal drug preparation* and *herbal medicinal product* in order to clarify the status of these

**Note for guidance**  
**„Quality of Herbal Medicinal Products“**

*GLOSSARY*

*Herbal medicinal products* are medicinal products containing as active substances exclusively herbal drugs or herbal drug preparations.

*Herbal drugs* are plants\* or part of plants in an unprocessed state, which are used for a medicinal or pharmaceutical purpose. A herbal drug or a preparation thereof is regarded as one active substance in its entirety whether or not the constituents with therapeutic activity are known.

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\* Thallophytes, especially lichens, higher fungi and algae are included

products. It can be expected that these texts will be included in the collection of European pharmaceutical legislation and rules as soon as possible.

This is a pragmatic way of the EMEA to implement the group's recommendations, and we do acknowledge the EMEA's continuous efforts to support our work despite a very difficult budgetary situation.

The group prepared a brief comment on the - *Draft CPMP Note for Guidance on Summary of Requirements to Active Substances in Part II of the Dossier* (Draft 4, CPMP/QWP/297/97). Similar comments may be necessary for future guidelines because the specific aspects of herbal drug preparations may not be addressed appropriately. Recent examples are the Notes for Guidance on stability testing of existing

active substances and for Type II variations from April 1998. These guidelines apply "to *chemical active substances and related finished products and not to radiopharmaceuticals, biologicals and products derived from biotechnology*". Herbal drug preparations are neither included nor excluded. The discussion how to adapt these guidelines to herbal drug preparations has already started. A dialogue is actively sought by both the CPMP Quality Working Party and our Working Group. With members of the Working Group being members of CPMP and CPMP working parties as well, an exchange of views and information should not be a problem, and major conflicts with established scientific standards can be excluded. Similar contacts with other CPMP working parties would be useful, especially with the Efficacy Working Party.

Confusion may arise from the publication of CPMP guidelines specifically devoted to new active principles. Many aspects addressed in these texts are relevant and valid for old substances as well. One example drafted in the ICH-process is the Quality note for guidance on specifications. The definitions of basic terms, reference to pharmacopoeias, requirements for specification, etc. are, in principle, valid for old substances and herbal drug preparations as well. One other example could be the CPMP note for guidance on fixed combinations. Evidently CPMP is mainly occupied by questions related to new active substances and biotech products. Most of the remaining time is consumed by pharmacovigilance issues. For this reason, preparing additional scientific guidance for herbal drug preparations in our working group might be a constructive way to improve harmonisation in the assessment of well established herbal products, to create more confidence in the European system and to facilitate mutual recognition. Such guidance is indispensable in the preclinical and clinical sector, because Article 1 of CD 75/318 states that in the case of bibliographic applications the provisions of the directive shall apply "*in like manner*". More than 23 years have passed since directive 75/318 was adopted and harmonised guidelines so that an explanation of what *in like manner* means would surely

not be premature. It is overdue. If one compares the translations of the term into the different languages of the Community it becomes evident that *in like manner* has no identical meaning. It is a reality that

**Council Directive 75/318 EEC  
of 20 May 1975**

*Article 1*

Where, pursuant to point 8 a) and b) of Article 4, second paragraph, of CD 65/65 EEC references to published data are submitted, the provisions of this Directive ***shall apply in like manner.***

(Germany: „sinngemäß“, France: „par analogie“)

lack of harmonised European guidance led to different interpretations and practices in Member States. Different interpretations of the so-called Scotia decision of the ECJ have added to the confusion. It was not a surprise for me when AESGP reported in January 1998 that AESGP members felt mutual recognition will probably not work with old substances. An enquiry made by EFPIA came to similar results.

### Safety guidance

The ad hoc working group discussed criteria for the preclinical assessment of herbal medicinal products and a guideline “Non-clinical testing of herbal drug preparations with long-term marketing experience - Guidance to facilitate mutual recognition and use of bibliographical data”- was drafted. Again, the second title makes it clear that it is not the aim of the group to propose a review of the national review or to criticise national approaches in the assessment of herbal medicinal products, but to protect public health and to facilitate access of adequately documented products to a common European market by eliminating obstacles to mutual recognition.

**NON-CLINICAL TESTING OF  
HERBAL DRUG PREPARATIONS  
WITH LONG-TERM MARKETING EXPERIENCE**  
*Guidance to facilitate mutual recognition  
and use of bibliographic data*  
September 1998

Effects that are difficult, even impossible to detect clinically

- Toxicity to Reproduction
- Genotoxicity
- Carcinogenicity

Expert-Report points out the necessity or not of new studies

The proposed guideline emphasises the need to address all the relevant questions set out by Part III of the Annex to Directive 75/318 EEC. It takes the available experience into account that has been gained with the use of well-established herbal drug preparations in humans, and defines conditions where additional studies may be required if an acceptable level of safety cannot be demonstrated by bibliographic data and experience in humans.

**NON-CLINICAL TESTING**

Tests not required, *if sufficient experience in humans is available:*

- ⇒ single dose toxicity,
- ⇒ repeated dose toxicity,
- ⇒ immunotoxicity
- ⇒ local tolerance testing
- ⇒ pharmacological tests including safety pharmacology,
- ⇒ pharmacokinetic studies.

The expert report must address these aspects and give the grounds why the documented medical experience justifies a safe use of the herbal drug preparation.

Considering the generally recognised problems with the scientific interpretation of bibliographic safety data, the heterogeneity of the interpretation of open terms of existing European legislation and the industry’s doubts about mutual recognition for old products, such guidance is indispensable for the function of the system. It must be clear, however,

that protection of consumer health is the priority and that the ticket to a European market will require efforts from industry as well. Harmonisation to the scientifically not justifiable minimum will not create a real common EU market, will not deliver value for money and will put consumers at risk. Exaggerated formalism in the interpretation of existing European legislation will add to the Europeans' reservation about "European bureaucracy". The criteria prepared by the working group allow a balanced view and guarantee that herbal medicinal products are assessed without negative prejudice and with a sense of proportion.

After discussion of comments presented by interested parties the CPMP was informed of the final document, which was released by the EMEA in September 1998.

### Efficacy guidance

The group went through Part IV of the Annex to Council Directive 75/318/EEC 'Clinical Documentation'. It turned out that Part 4 will need additional discussion and guidance in its interpretation for bibliographic applications. The reason is that Part IV, in some paragraphs, addresses exclusively the situation of new prospective controlled clinical trials and not the interpretation of bibliographic data or

Part 4 of Annex to  
Council Directive 75/318/EEC  
of 20 May 1975  
"Clinical documentation"

Terminology not well adapted to bibliographic applications. Documentation on experience in the form of epidemiological studies can be taken into account in bibliographical applications for well-established medicinal products.

epidemiological studies such as non-interventional studies. This may result in conflicting interpreta-

tions of the same bibliographic documents or epidemiological studies.

Although efficacy was recognised as being the most difficult issue, the group agreed on some general principles and reached agreement on a first draft of a core SPC for *Valerianae radix*. The group considered that the drafting of such core SPCs on

core-SPC for  
**VALERIANAE RADIX**  
(September 1998)

2. *QUALITATIVE AND QUANTITATIVE COMPOSITION*  
Valerian root  
Extract prepared with water, ethanol/water (max 70%)  
Tinctures (1:5, ethanol 70% V/V)

4.1. *THERAPEUTIC INDICATIONS*  
*Herbal medicinal product* for the relief of temporary nervous tension and temporary difficulty in falling asleep.

the basis of selected ESCOP monographs would be the most appropriate way to develop general guidance on criteria to assess efficacy data based on bibliographical documentation for herbal medicinal products. Specific points of concern were the lack of bibliographic data on the use of herbal medicinal products in young children and some monographs that cover a broad range of different forms of administration and indications, e.g. external use, oral use, inhalation etc. One other point of interest was the discussion of therapeutic alternatives in the case of more serious indications such as hypercholesterolemia, colitis or depression.

In order to make a point of the particular character of herbal drug preparations it was proposed to start the paragraph on indications in the SPC and in the package leaflet by a term such as "herbal medicinal product for ...".

After discussion of comments presented by interested parties, the final core SPC on valerian and comments on part 4 of the annex to Directive 75/

318 EEC were presented to CPMP and released by the EMEA in September 1998.

### Fixed Combinations

The use of fixed combinations is one characteristic aspect of phytotherapy. Because the CPMP note for Guidance is devoted to new fixed combinations, criteria for the assessment of herbal fixed combinations had to be drafted by the group. The draft Note for Guidance makes it clear that exaggerated requirements, such as multiple clinical trials for well known fixed combinations of herbal drug preparations, have to be avoided. Nevertheless, there must be an adequate and proportionate justification of the fixed combination considering both the indications claimed for the product and the risks due to the ingredients. Each active ingredient must contribute to the overall safety and/or efficacy of the fixed combination. Irrational fixed combinations will not be acceptable for an European marketing authorisation.

The draft guideline was presented to CPMP for information and released by the EMEA in September 1998 for comment by December 1<sup>st</sup> 1998.

### Advice given to the European Pharmacopoeia

One other interesting aspect of the group is the possibility to exchange requirements and experiences between assessors and the European Pharmacopoeia. The group underlined the urgent need for a general monograph on herbal drugs in the European Pharmacopoeia. Drafts prepared by the European Pharmacopoeia were discussed and comments for modification were given. Additionally the group advised the European Pharmacopoeia on the safe use of the tincture of *Salvia*.

### Pharmacovigilance

At the last meeting in November 1997 ESCOP presented to the working group their pharmacovigilance study of herbal medicinal products. The group acknowledged the effort made by ESCOP to collect

clinical safety data for herbal drugs. These data could be useful in future discussions on core-SPCs. Because herbal medicinal products are subject to pharmacovigilance regulations as set out by Directives any interference with these systems in force has to be avoided.

### Current and Future Activities

During the two meetings in 1998 new questions related to the pharmaceutical and clinical documentation were discussed. Major topics were the draft stability guidelines and the guideline on specifications. It turned out that the CPMP guideline for specifications has to be adapted to herbal drug preparations. Clarification of this issue will be necessary for future discussions on other legal issues, e.g. variations.

On the basis of a global assessment of ESCOP monographs some monographs were selected that will be assessed and discussed in detail in order to prepare harmonised core-SPCs and general criteria for the assessment of bibliographic data on efficacy. Members of the group were appointed rapporteur and ESCOP was addressed to send the documentation of these monographs to the rapporteur and to the EMEA.

Preparation of criteria for the categorisation and assessment of bibliographic data will be based on the national experiences of the Member States gathered during the review of old substances and on the need to give an interpretation of open terms in European legislation. An interesting approach to classify the different levels of evidence of efficacy was presented by the US Agency for Health Care Policy and Research. The paper makes it clear that there are different levels of evidence in medicine. These categories could be a starting point for clarification of the term “*in like manner*” of Directive 75/318 EEC.

<b>Levels of Evidence</b>	
US Agency for Health Care Policy and Research 1992	
<b>Level</b>	<b>Type of Evidence</b>
Ia	Meta-analysis of randomized controlled trials
Ib	at least one randomised controlled trial
IIa	at least one well-designed controlled study without randomisation
IIb	at least one other type of well-designed quasi-experimental study
III	well-designed non experimental descriptive studies, such as comparative studies, correlation studies, case-control studies
IV	expert committee reports or opinions and/or clinical experiences of respected authorities.

These activities were started by the group despite the uncertainties related to the future work of the group and the frustration that resulted from the decision of the EMEA to cancel the third meeting scheduled for November of this year for budgetary reasons. The useful results achieved within a short time demonstrate the high engagement of all participants. However, the group needs a clear framework for future work and a clearly defined status as well. This includes continued organisational support by the EMEA, backed up by a budget.

There are many arguments in favour of a continua-

tion and implementation of a permanent group: The need remains to address the specific aspects of herbal medicinal products in European legislation and expertise is needed to do so. The availability of such expertise will increase industry's and consumer's confidence in the European system. It is possible to find common-sense solutions within the existing European legislation. Finally, development of transparent criteria for the assessment of bibliographic documentation 23 years after the introduction of Directive 75/318 is not premature but overdue.

I do not want to end this presentation without thanking ESCOP for their excellent co-operation. Without the involvement of the ESCOP scientists we would not have been able to reach progress in the area of herbal medicinal products so quickly. The work of ESCOP has demonstrated that it is possible to make high-level scientific assessment of herbal medicinal products. ESCOP monographs are an essential element in a balanced assessment of herbal medicinal products. They make an important contribution to consumer protection by giving honest information on the safety and efficacy of herbal drug preparations and by offering an alternative to misleading "traditional" or "structure-function" claims.

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